Undetectable measured serum bicarbonate associated with hypertriglyceridemia-induced pancreatitis

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A 48-year-old woman presented to the emergency department with 12 hours of nausea, vomiting and epigastric pain radiating to her back. The pain worsened with movement and inspiration and improved with bending forward. She had no change in her bowel habits, polydipsia or polyuria. Her medical history included suboptimally controlled type 2 diabetes mellitus diagnosed 3 years previously (glycosylated hemoglobin [HbA_{1c}] 8.9% [reference range 4.0%–6.0%]) and cholecystectomy. She was taking metformin 1000 mg twice daily.

She had a 25-pack-year history of cigarette smoking and smoked marijuana daily. Her alcohol ingestion had increased over the past 6 months to 8 to 10 drinks of hard liquor (1.5 oz) per week. She indicated that she had not consumed alcohol during the week before her presentation; she ate fast food daily. Her family history included hypercholesterolemia and type 1 and type 2 diabetes; there was no history of premature cardiac disease.

On examination, the patient was tachycardiac (111 beats/min), normotensive and afebrile with no Kussmaul breathing. Despite having a jugular venous pressure of 7 cm H_2O, she had dry mucous membranes and was considered to be clinically volume depleted. On abdominal examination, she had epigastric tenderness. She had no eruptive xanthomas.

Laboratory investigations showed hyperglycemia (blood glucose 16.7 [normal 4–7] mmol/L) and hyponatremia (serum sodium 129 [normal 133–145] mmol/L) (Box 1). The patient's sodium level corrected for hyperglycemia was 132 mmol/L. Her bicarbonate level measured as an electrolyte (TCO_2) was undetectable, but her calculated bicarbonate (HCO_3^-) levels on both arterial and venous blood gases were normal at 23 and 20 mmol/L, respectively. Manual calculation of the anion gap using TCO_2 of 0–5 mmol/L was 27–22 (normal 10–14) mmol/L. She had mildly elevated lactate, β-hydroxybutyrate levels and elevated osmolar gap (25 [normal < 10] mmol/kg). Lipase was elevated (318 {normal < 79] U/L). Serum volatile alcohols, salicylates, ethanol and acetaminophen were undetectable. Blood gases were measured on a GEM 4000 Analyzer, serum osmolarity on an Advanced Micro-Osmometer Model 3320, HbA_{1c} on a VARIANT II analyzer and other biochemistry measured on an Abbott Architect C16000. A CT of the abdomen and pelvis showed findings consistent with diffuse pancreatitis with peripancreatic inflammatory changes and fluid extending to the retroperitoneum/right upper quadrant with reactive segmental thickening of the hepatic flexure

KEY POINTS

- Hypertriglyceridemia can lead to a substantial discordance in measured (TCO_2) and calculated (HCO_3) serum bicarbonate levels on serum electrolyte testing and blood gases, respectively.
- Hypertriglyceridemia can interfere with laboratory assays, making the HCO_3 value on blood gas analysis a more reliable and accurate measure of acid-base status than the TCO_2 value.
- Patients with suboptimally controlled diabetes presenting with hypertriglyceridemia-induced pancreatitis may have a clinical picture similar to that seen in patients with diabetic ketoacidosis.

The patient's clinical presentation and elevated lipase were consistent with acute pancreatitis. However, her metabolic derangements were puzzling, given the undetectable TCO_2 tested on serum electrolytes and normal HCO_3^- on the blood gas analysis. Despite the clinical picture and pH being more consistent with the normal HCO_3^-, our decision-making was based on the TCO_2 level being more accurate (the patient would be at high risk of rapid clinical deterioration if the HCO_3^- was incorrectly presumed to be accurate).

The differential diagnosis for the patient's anion gap metabolic acidosis included diabetic ketoacidosis on a background of type 1 rather than type 2 diabetes, or lactic acidemia secondary to dehydration, sepsis or metformin. Given the patient's hyperglycemia, elevated anion gap, elevated ketones and no alternate explanation, we admitted her to the step-down unit with a diagnosis of acute pancreatitis and diabetic ketoacidosis.

After 2 L of intravenous normal saline, the patient's sodium level remained stable at 130 mmol/L and anion gap was 21–26 mmol/L. Rapid overcorrection of her sodium level was not a concern as the hyponatremia was largely pseudohyponatremia. We treated her with intravenous normal saline at 125–250 mL/hour and intravenous insulin at 4 units/hour as per our

Box 1: Results of laboratory investigations in a 48-year-old woman with pancreatitis secondary to hypertriglyceridemia

Laboratory parameter	Reference range, adult	Presentation (day 0, hour 2)	Pre-apheresis (day 1)	Discharge (day 5)
Na, mmol/L	133–145	129	134	136
Corrected Na for hyperglycemia, mmol/L*	133–145	132	136	137
Theoretical corrected Na for hyperlipidemia, mmol/L†	133–145	134	NA‡	137
K, mmol/L	3.7–5.3	3.5	2.9	3.6
Cl, mmol/L	97–110	102	105	102
TCO_2, mmol/L	19–27	< 5	16	23
Anion gap, mmol/L	8–12	NA	13	11
Creatinine, µmol/L	0–110	33	22	35
Blood glucose, mmol/L	3.5–11.1	16.7	13.1	9.5
Albumin, g/L	35–55	28		22
Calcium, mmol/L	2.25–2.80	2.00	1.65	2.12
Lipase, U/L	0–79	318		
Lactate, mmol/L	0.5–2.2	2.6	3.1	1.3
Osmolality, mmol/kg	281–297	302	292	
Osmolar gap, mmol/kg		25.1		
Venous blood gas				
pH	7.32–7.43	7.33	7.49	7.35
pCO_2, mmHg	40–50	44	32	45
HCO_3, mmol/L	22–29	23	24	25
Arterial blood gas				
pH	7.35–7.45	7.30		
pCO_2, mm Hg	35–45	40		
pO_2, mm Hg	80–100	56		
$pHCO_3$, mmol/L	21–27	20		
Triglycerides, mmol/L	0–1.70	36.78	23.68	2.33
Cholesterol, mmol/L	0–5.20	16.00		3.57
HDL cholesterol, mmol/L	1.20–5.00	0.55		0.23
β-hydroxybutyrate, mmol/L	0–0.37	0.54		< 0.20
HbA_{1c}, %	4.0–6.0			8.9
TSH, mIU/L	0.40–4.50		0.76	

Note: Cl = chloride, HbA_{1c} = glycosylated hemoglobin, HCO_3 = calculated bicarbonate, from blood gas sample, HDL = high-density lipoprotein, K = potassium, Na = sodium, PCO_2 = partial pressure of carbon dioxide, $PHCO_3$ = concentrate of bicarbonate in plasma, TCO_2 = measured serum total CO_2, from serum electrolytes sample, TSH = thyroid-stimulating hormone.
*Corrected [Na+] = measured [Na+] + 3/10 × ([plasma glucose (mmol/L)]-5).[1]
†Calculation based on proposed formula: Corrected [Na+] = measured [Na+] + total lipids/10.[12] There is no consensus on a correction factor in the literature.
‡Corrected sodium for hyperlipidemia cannot be accurately calculated, as total cholesterol was not available for this time period.

institution's diabetic ketoacidosis protocol. Given our concern about the undetectable TCO_2, we administered a sodium bicarbonate infusion at 150–200 mL/hr despite normal pH; this was not in keeping with diabetic ketoacidosis treatment guidelines.[1] The laboratory technician reported the patient's blood sample to be lipemic and her lipid panel showed severe hypertriglyceridemia (36.78 [normal 0–1.70] mmol/L).

Very low high-density lipoprotein (HDL), high cholesterol levels and markedly elevated triglyceride levels (Box 1) suggested hypertriglyceridemia as the cause of her pancreatitis. We consulted the endocrinology service. Based on the normal calculated HCO_3^- and pH, we diagnosed hyperglycemia as β-cell dysfunction from acute pancreatitis rather than diabetic ketoacidosis. The similarities between hypertriglyceridemic pancreatitis and diabetic ketoacidosis include abdominal pain, nausea or vomiting, dehydration, tachycardia, hyperglycemia, pseudohyponatremia, low serum bicarbonate levels and a wide anion gap. The diabetic ketoacidosis protocol was discontinued, and the patient was transitioned to subcutaneous insulin for diabetes management.

The patient's triglycerides improved (23.68 mmol/L) with bowel rest, intravenous fluids and insulin, but she remained clinically unwell with abdominal pain and vomiting. Because she became hypocalcemic at 1.65 mmol/L (Box 1), we began apheresis to lower her triglycerides rapidly. We inserted a hemodialysis line and she underwent 1 round of apheresis with marked improvement. The patient's triglyceride level (3.45 mmol/L) improved, as did her TCO_2 (19 mmol/L). She was started on fenofibrate 200 mg/d, rosuvastatin 20 mg/d and omega-3 fish oil 2–3 g/d. Metformin was resumed at 1000 mg twice daily.

The patient was discharged after 5 days, with insulin glargine 12 units nightly. At discharge, her triglycerides level was 2.33 mmol/L and her TCO_2 was normal at 23 mmol/L. We did not undertake genetic testing for primary causes of hypertriglyceridemia as her diet, alcohol intake and diabetes were contributing secondary factors requiring control. The patient's markedly low serum HDL level was nonspecific, possibly related to metabolic syndrome, acute inflammation or primary hyperlipidemia. Follow-up with her family physician and endocrinology was arranged.

Discussion

Risk factors for hypertriglyceridemia-induced pancreatitis

Hypertriglyceridemia results from a combination of primary (genetic) and secondary causes. Secondary causes include metabolic syndrome, suboptimally controlled diabetes (often type 2) from insulin resistance and excess alcohol intake.[2]

Although mild or moderate hypertriglyceridemia is a risk factor for cardiovascular disease, hypertriglyceridemia is not an important risk factor for pancreatitis until severe (> 11.2 mmol/L), which is uncommon in isolated acquired hypertriglyceridemia.[2] Therefore, in patients with hypertriglyceridemia-induced pancreatitis, underlying primary disorders of lipid metabolism must be considered.[2]

Patients who develop hypertriglyceridemia-induced pancreatitis tend to have acute-on-chronically elevated serum triglycerides triggered by uncontrolled secondary factors such as

diabetes mellitus, pregnancy or heavy alcohol consumption.[3–5] Diabetes mellitus underlies 62% to 79% of cases of hypertriglyceridemia-induced pancreatitis.[3,4]

Clinical presentation and diagnosis

The clinical presentation of hypertriglyceridemia-induced pancreatitis is similar to pancreatitis of other causes; however, there is higher risk of organ failure and admission to the intensive care unit in hypertriglyceridemia-induced pancreatitis.[5,6] The Revised Atlanta Criteria for diagnosing acute pancreatitis require at least 2 of the following: abdominal pain consistent with acute pancreatitis; serum lipase or amylase ≥ 3 times the upper limit of normal; and characteristic findings of acute pancreatitis on imaging studies.

Hypertriglyceridemia-induced pancreatitis constitutes 2%–10% of cases of acute pancreatitis. It is often overlooked for more common causes, including gallstones and alcohol.[5] However, as noted earlier, alcohol abuse has been identified as a risk factor for recurrent hypertriglyceridemia-induced pancreatitis (hazard ratio 3.40 [95% confidence interval 1.37-8.42]).[4] Another confounder in diagnosis is the epiphenomenon of a mild-to-moderate elevation of serum triglycerides observed in up to 33% of acute pancreatitis of all causes.[7] That said, observational data suggest that the incidence of hypertriglyceridemia-induced pancreatitis with serum triglycerides < 20 mmol/L is uncommon (< 5% of cases).[2,5]

Laboratory findings

Laboratory findings in hypertriglyceridemia-induced pancreatitis are similar to those seen in acute pancreatitis of other causes, with several notable differences. Pseudohypobicarbonatemia, defined as a discrepancy between HCO_3^- and TCO_2 that occurs mainly secondary to laboratory interference, has been well described (Box 2).[8,9] In our institution, enzymatic spectrophotometric methods are employed for electrolyte measurement. In this type of assay, large particles such as chylomicrons and very low-density lipoproteins absorb light and cause light-scattering interference during analysis. This leads to falsely low TCO_2 values.[8,9] In contrast, the bicarbonate value in a blood gas sample is calculated from the blood pH and partial pressure of CO_2, which are not subject to the same interference.

Pseudohyponatremia is also seen in hypertriglyceridemia. The indirect ion-selective electrode technique is used for electrolyte measurement in our hospital. With this method, specimens are diluted before electrolyte measurement. With substantial volume displacement in severe hyperlipidemia, results can yield falsely low electrolyte concentrations, leading to pseudohyponatremia. Lipemic specimens can be cleared by ultracentrifugation or pretreatment with a reagent before analysis.[8,10]

A formula for calculating corrected sodium levels has been proposed:[11] corrected $[Na^+]$ = measured $[Na^+]$ + (total lipids/10), where $[Na^+]$ and total lipids (cholesterol and triglycerides) are in mmol/L.

Finally, an elevated anion gap has been reported in patients with severe hypertriglyceridemia and pseudohyponatremia; this is thought to be caused by excess lipolysis-producing hydrogen ions, which titrate out serum HCO_3^-.[8,9] It is crucial for clinicians to be aware of these laboratory interferants to arrive at the correct diagnosis.

Box 2: Differential diagnosis of discordance between measured TCO_2 and calculated HCO_3[10,13]

Underlying cause	Value affected
Sample handling error	
Excess heparin in blood gas sample	↓HCO_3
Loss of anaerobic conditions in sample	↓TCO_2
Calibration error or machine imprecision	↓/↑ HCO_3 and TCO_2*
Medical conditions	
Hypertriglyceridemia	↓ TCO_2
Paraproteinemia	↓ TCO_2
Organic acids (e.g., lactic acidosis, diabetic ketoacidosis)	↓TCO_2
Critical illness, low bicarbonate concentrations ≤ 20 mmol/L	↓/↑ TCO_2

Note = HCO_3 = calculated bicarbonate (from blood gas sample), TCO_2 = measured serum total CO_2 (from serum electrolytes sample).
*These errors are rare and usually identified before release of results.

Management

There is no evidence-based clinical practice guideline for management of hypertriglyceridemia-induced pancreatitis. Conservative therapy includes bowel rest, fluid resuscitation and pain management. Insulin infusion has been described as a safe and effective treatment strategy in patients with and without diabetes.[3,6] Insulin activates lipoprotein lipase enzyme to enhance chylomicron degradation and lower the triglyceride level[3,6]

Intravenous heparin also enhances lipoprotein lipase enzyme activity, and can be used synergistically to lower triglycerides in severe pancreatitis.[3,6] Intermittent bolus doses are preferred over continuous infusion to reduce bleeding complications and rebound hypertriglyceridemia from lipoprotein lipase depletion.[3,6]

Apheresis has been described as an effective option for symptomatic relief from rapid triglyceride reduction and reduction of inflammation.[6] However, recent studies have shown no benefit in clinical outcomes and possible complications such as allergic reactions and infusion-related infection.[3,6]

Long-term management options include nonpharmacologic (dietary modification, exercise and weight reduction) and pharmacologic measures (fibrates, niacin and omega-3 fatty acids with or without statins).[2]

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